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08/426,509 04/21/95 ULLRICH

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EXAMINER
TENIST-S

18M1/0610

ART UNIT 1812

PENNIE & EDMONDS
1155 AVENUE OF THE AMERICAS
NEW YORK NY 10036-2711

1812

DATE MAILED 06/10/96

This is a communication from the examiner in charge of your application
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 3/25/96 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐

Part II SUMMARY OF ACTION

1. ☒ Claims 1-30 are pending in the application

Of the above, claims 1-13 and 23-30 are withdrawn from consideration

2. ☐ Claims have been cancelled.

3. ☐ Claims are allowed.

4. ☒ Claims 14-16 and 18-22 are rejected.

5. ☒ Claims 17 is objected to.

6. ☒ Claims 1-30 are subject to restriction or election requirement

7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☒ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

1. Applicant's election with traverse of Group III, claims 14-22, in Paper No. 10, is acknowledged. The traversal is on the ground(s) that Inventions I through V are inextricably intertwined and closely related. This is not found persuasive because the traverse does not adequately address or point out the supposed errors in the restriction requirement (see MPEP 818.03(a) and (c)). Applicant's argument does not in any way relate to the examiner's reasons--distinctness and separate classification--set out in accord with MPEP 806.05(e). In order to overcome the reasons set forth by the examiner, applicant must point out the nature of such relationship. The examiner agrees with the applicant that the invention in the different restriction groups are related. However, the test for propriety of restriction is not whether the inventions are related but rather whether they are distinct and whether it would impose a burden on the examiner to search and examine multiple inventions in a single application. Although the antisense oligonucleotides can be obtained from the full length nucleotide sequence, the antisense oligonucleotide can also be obtained by PCR reaction amplifying cDNA from megakaryocytes. The protein and antibodies are structurally and functionally distinct products, even though the antibodies interact with the protein. Further, each of the inventions requires separate considerations with respect to issues of patentability. Clearly, it would impose a burden on the examiner to search all the inventions in one application.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 15, 17, and 19 are objected to as not complying with §1.821(d) of the Sequence Rules and Regulations. When the description or claims of a patent application discuss a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulation, reference must be made to the sequence by use of the assigned identifier, in the text of the description and claims of the patent application. Claims 15, 17, and 19 refer to sequences by their figure numbers instead of their sequence identifiers. It is suggested that the figure numbers be deleted from the claims and that the claims refer to the claimed sequences by their sequence identifiers.

3. Claims 14, 16, 18, and 20-22 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to MKK1 comprising SEQ ID NO: 2, MKK2 comprising SEQ ID NO: 4, and MKK3 comprising SEQ ID NO: 6. See M.P.E.P. §§ 706.03(n) and 706.03(z).

The specification does not enable all polypeptides encompassed by the names "MKK1", "MKK2", and "MKK3". The name or abbreviation for a protein is subject to change, and one name often can refer to multiple products. For example, MKK can stand

for map kinase kinase which is a different protein from the MKKs disclosed in the specification. Besides, megakaryocytic kinases are referred to as HYL by Sakano et al., matk by Bennett et al., FRK by Lee et al., and TK1 or RAK by Cance et al. Additionally, the name MKK encompasses modified and mutant forms of the protein which are not enabled by the specification because there is insufficient guidance as to how to obtain MKK mutants. The specification neither discloses amino acids that can be altered without affecting the functional activity of the protein nor teaches residues that are essential for activity. Although it is within the skill of the artisan to obtain MKK mutants, it would require undue experimentation of the skilled artisan to obtain mutants with functional activity in the absence of sufficient guidance. The skilled artisan would have to obtain mutants by randomly altering residues; however, random amino acid alterations can change the functional activity of the protein or render it inactive.

To overcome this rejection, it is suggested that the claims be amended to recite the enabled MKKs by including amino acid sequence or nucleic acid sequence that are disclosed in the specification.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out

region of MKK3. Based on the identity of the partial amino acid sequences, one would have expected the full length TK1 and MKK3 to be identical proteins. However, Cance neither discloses the full length cDNA clone encoding TK1 nor teaches the TK1 polypeptide.

The teachings of Sambrook are discussed above.

Given that Cance teaches that TK1 is expressed at high levels in BT20 cell lines, it would have been obvious to the skilled artisan at the time the invention was made to use the partial cDNA of Cance as a probe to screen a BT20 cDNA library with the expectation of isolating the full length TK1 cDNA. It would also have been obvious to subclone the isolated full length DNA into an expression vector and to transfect the vector into a host cell for production of large quantities of the protein, as taught by Sambrook. The motivation to obtain the polypeptide is provided by Cance who teaches that src kinases play an important role in the pathogenesis of cell cycles (page 571).

Thus, the claims are *prima facie* obvious over the prior art.

8. Claim 20 is rejected under 35 U.S.C. § 103 as being unpatentable over Bennett et al. in view of Maniatis et al.

The teachings of Bennett are discussed above. However, Bennett does not disclose a fusion protein comprising matk (MKK1) linked to a heterologous protein or peptide sequence.

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --
(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 14 and 15 are rejected under 35 U.S.C. § 102(a) as being anticipated by Bennett et al.

Bennett teaches isolation of the DNA encoding matk, a nonreceptor tyrosine kinase isolated from a human megakaryoblastic cell line and discloses its DNA and amino acid sequences (abstract and fig. 1). Although the disclosed protein is not called MKK1, the amino acid sequence of the disclosed protein is identical to SEQ ID NO: 2 of the presently claimed MKK1. Accordingly, they are the same product. In figure 5, Bennett shows the isolated matk protein obtained by *in vitro* transcription and translation of its encoding DNA and purification comprising SDS-PAGE. Thus, the claims are anticipated by Bennett et al.

6. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 18 and 19 are rejected under 35 U.S.C. § 103 as being unpatentable over Lee et al. in view of Sambrook et al.

Lee teaches isolation of the DNA encoding FRK, a novel nonreceptor protein tyrosine kinase from human hepatoma cell line and discloses the DNA and the deduced amino acid sequences of FRK (abstract and page fig. 1). Although the disclosed protein is not called MKK3, the deduced amino acid sequence of FRK is identical to SEQ ID NO: 6 of the presently claimed MKK3. Thus, they must be the same product. However, Lee does not disclose the FRK polypeptide.

Sambrook teaches method steps for expression of isolated genes in mammalian cells and *E. coli* (Vol. 3, Chapter 16 and 17). The method of Sambrook involves subcloning the desired gene into an expression vector and transfecting the expression vector into a host cell. Sambrook also discloses expression vectors comprising transcriptional elements, such as promoter, enhancer,

or termination and polyadenylation signals appropriate for mammalian or bacterial host cell expression (Fig. 16.1 A-F, 16.3 A-C, 16.6 A-B and page 17.11-17.28).

Accordingly, it would have been obvious to the skilled artisan at the time the invention was made to subclone the isolated FRK cDNA of Lee into an expression vector and transfect the expression vector into a host cell for expression of FRK polypeptide, as taught by Sambrook et al., with the expectation of obtaining large quantities of the polypeptide for structure function studies. The motivation to obtain the polypeptide is provided by Lee who teaches that nonreceptor tyrosine kinases play an important role in cell proliferation and differentiation.

Thus, the claims are *prima facie* obvious over the prior art.

7. Claims 18 and 19 are rejected under 35 U.S.C. § 103 as being unpatentable over Cance et al. (1993) in view of Sambrook et al.

Cance discloses isolation of a partial cDNA clone encoding TK1, a protein tyrosine kinase (abstract and Table II). Cance et al. show that TK1 is expressed at high levels in breast cell lines BT20 and SK-BR3 and is a member of the src family of kinases (page 573 and fig. 1). Even though the prior art does not disclose the complete amino acid sequence of TK1, a comparison of the partial TK1 amino acid sequence with that of MKK3 of the present application suggests that the disclosed partial amino acid sequence is identical to the corresponding

Maniatis teaches expression of fusion proteins and discloses vectors suitable for expression of fused eucaryotic proteins (pages 422-430). Maniatis also discusses the advantages of fusion proteins, such as stability in bacteria (page 422).

Accordingly, it would have been obvious to the skilled artisan to modify the matk protein of Bennett by fusing it to a heterologous protein by following the method of Maniatis, with the expectation of obtaining a high yield of the matk protein from *E. coli*. The motivation to obtain matk fusion protein is provided by the Maniatis who discloses the advantages of fusion proteins.

Thus, the claims are *prima facie* obvious over the prior art.

9. Claim 22 is rejected under 35 U.S.C. § 103 as being unpatentable over Lee et al. or Cance et al. (1993) in view of Maniatis et al.

The teachings of Lee and Cance are disclosed above. However, neither Lee nor Cance discloses fusion proteins comprising FRK or TK1 (MKK3) and a heterologous polypeptide.

The teachings of Maniatis are discussed above.

Accordingly, it would have been obvious to the skilled artisan to modify the FRK protein of Lee or the TK1 protein of Cance by fusing it to a heterologous protein by following the method of Maniatis, with the expectation of obtaining a high yield of the fusion protein from *E. coli*. The motivation to

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obtain FRK or TK1 fusion protein is provided by the Maniatis who discloses the advantages of fusion proteins.

Thus, the claims are *prima facie* obvious over the prior art.

10. Claim 17 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 16 would be allowable if rewritten or amended to overcome the rejection under 35 U.S.C. 112.

Any inquiry concerning this communication should be directed to Sally Teng, Ph.D., at telephone number (703) 308-4230. The examiner can normally be reached on Monday-Thursday from 8:30 to 6:00. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, G. Draper, can be reached at telephone number (703) 308-4232.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-0294.

Sally P. Teng
June 3, 1996 *SP*


GARNETTE D. DRAPER
SUPERVISORY PRIMARY EXAMINER
GROUP 1800